Monday, March 4, 1991
2:00PM–3:30PM, Room 202, East Concourse
Electrophysiology: Basic

2:00
PREVENTION OF Ca^{2+}-OVERLOAD CAUSED BY DISTURBED Na^+ CHANNEL INACTIVATION

Luc Ver Donck, Frieda Bielen*, Hugo Geerts, Marcel Borgers, Fons Verdonck*. Janssen Research Foundation, B-2340 Beerse and *University of Leuven, Campus Kortrijk, B-8500 Kortrijk, Belgium

Previous work has shown that Ca^{2+}-overload may be mediated by impaired Na^+ channel functioning: intracellular Na^+ (Na_i^+)-load as a consequence of impaired Na^+ channel inactivation activates Na^+/Ca^{2+}-exchange, resulting in Ca^{2+}-overload (*J Mol Cell Cardiol 22 (Suppl 3) S.11, 1990*). We examined the action of the cardioprotective drug R 56865 (R) (*N-[1-[4-(4-fluorophenoxy)butyl]-4-piperidinyl]-N-methyl-2-benzothiazol-amine*) on the veratridine (V) modified Na^+ channel of rabbit myocytes and Purkinje cells. V is a veratrum alkaloid that also slows Na^+ channel inactivating kinetics. TTX (3.10^{-5} M)-sensitive Na^+ currents were measured with the whole cell recording technique. Inactivation of the Na^+ current evoked by depolarizing pulses was markedly slowed by V (1.10^{-5} M) and a steady inward current was present at holding potentials (V_h) between -20 and -80 mV. R potently blocked the V modified current changes in a potential dependent way. The steady-state TTX-sensitive inward Na^+ curent was dose-dependently blocked by R : 80% of the current was suppressed by 1.10^{-6} M R at V_h -20 mV. The blocking effect progressively decreased with more negative V_h. Although R partially suppressed the V-induced Na^+ current evoked by depolarizing pulses starting from -80 mV, the blocking potency was much less than in continuously depolarized cells. The drug's strong potential dependency agrees with its minor effects on the normal action potential configutration and the absence of local anesthetic effects. Na_i^+ was determined by SBFI-fluorescence, a Na_i^+ sensitive fluorescent probe. R (2.10^{-7} M) reduced the V-induced gain in Na_i^+ to near baseline Thus, part of the cardioprotective effects of R may be related to its action on the gain in Na_i^+ under conditions of increased bursting of the Na^+ channel, a: may occur in ischemic cells.

2:15
CHARACTERIZATION OF SODIUM CHANNEL BLOCK BY MORICIZINE IN CARDIAC PURKINJE FIBERS

James Coromilas, M.D., F.A.C.C., and Huan-Lin An, M.D. Columbia University, New York, N.Y.

Moricizine is the only antiarrhythmic drug being studied in the Cardiac Arrhythmia Suppression Trial yet it's electrophysiologic properties remain incompletely characterized. The purpose of this study was to characterize the kinetics and voltage dependence of sodium (Na) channel block by moricizine. Vmax was used as an index of available Na current in goat Purkinje fibers. We used a two microelectrode voltage clamp to apply conditioning pulses of varying duration and measured Vmax 100 msec after the conditioning pulse to determine the magnitude and rate of onset of inactivation block. The voltage clamp was also used to control resting and plateau voltage, action potential duration (APD), and recovery interval during trains of action potentials (AP). Moricizine (1 mg/liter) produced a 8 mV hyperpolarizing shift of the steady state Vmax-voltage relationship. No block occurred during the AP upstroke but block occurred slowly (τ = 5.0±1.7 sec) during a conditioning pulse at -25mV. During AP trains with a 500 msec cycle length, 310 msec plateau at -30mV, and 190 msec recovery interval at -80 mV, frequency-dependent depression of Vmax occurred with a τ of 5.4±2.3 sec. In contrast, during AP trains with a 200 msec cycle length, no plateau, and the same 190 msec recovery interval, there was negligible frequency-dependent depression of Vmax. Recovery from block occurred with a τ of 3.1±0.4 sec and was not enhanced by channel opening. In conclusion, moricizine has recovery kinetics that are slower than those of the currently available IB drugs and faster than those of the currently available IA drugs. Moricizine blocks Na channels during the AP plateau and not during the AP upstroke. This inactivation block is characteristic of IB and not IA drugs. However, because inactivation block occurs slowly during each AP plateau and unblocking during the recovery interval is slower, the rate of onset of frequency-dependent depression of Vmax during AP trains is slower and occurs at longer cycle lengths with moricizine than with other IB drugs. Moricizine is best characterized as a Class IB drug with kinetics at the slow end of the IB spectrum.

2:30
MECHANISM OF ACTION OF CLASS III DRUGS ON REENTRANT VENTRICULAR TACHYCARDIA IN ANISOTROPIC MYOCARDIUM

Josep Brugada, Lucas Boersma, Denis Escande, Charles Kirchhof, Maurits Allessie. Department of Physiology, University of Limburg, Maastricht, The Netherlands.

The effects of RP62719, a new class III drug, were studied on reentrant ventricular tachycardia (VT) in an anisotropic ring of perfused rabbit hearts. In 4/8 hearts, 0.03 μM of the drug terminated VT. Prior to termination cycle length increased from 145±15 to 172±29 ms, V refractory period (VRP) prolonged from 110±11 to 160±27 ms and the excitable gap (EG) decreased from 38±10 to 12±7 ms. Termination was due to collision of the VT wavefront with a reflected beat. In 4/8 hearts despite administration of 0.03, 0.3 and 3.0 μM of the drug, VT did not terminate. The cycle length remained stable at 0.03 and 0.3 μM (186±19 ms) but increased to 249±19 ms at 3.0 μM. At 0.03, 0.3 and 3.0 μM the VRP prolonged from 107±20 to 136±22, 150±17 and 202±21 ms and the EG decreased from 79±22 to 57±25, 50±18 and 46±5 ms respectively. Conduction velocity only was modified at 3.0 μM. Longitudinal and transverse conduction velocity respectively decreased from 64±2 to 55±3 cm/s and from 22±1 to 15±2 cm/s. During control, VT that terminated had shorter cycle length and narrower EG than VT that did not terminate (p<0.01). Conclusion: RP62719 acts as a pure class III drug at 0.03 and 0.3 μM. In fast VT's, prolongation in VRP almost completely closes the EG. Local prolongation in VRP induces reflected beats that collide with the reentrant beat and terminate VT.

2:45
VENTRICULAR TACHYCARDIA INDUCED BY FLECAINIDE ACETATE IN THE NORMAL CANINE HEART

Hiroshi Tsunakawa, Kensuke Imai, Bunken Ebato, Tetsuro Shirai, Saburo Mashima. Showa University Fujigaoka Hospital Yokohama, Japan

Effect of Flecainide Acetate(FA) on ventricular tachycardia(VT) induction was studied in relation to anisotropic conduction and dispersion of refractoriness in 10 normal dogs. Anisotropic conduction velocity and refractory period(RP) were determined using a 48-electrode plaque on the right ventricular epicardial surface. FA with plasma concentration of therapeutic range (FA(1)) decreased the conduction velocity(CV) both along (longitudinal;L) and across (transverse;T) the fiber orientation with greater reduction in the L direction (%CV decrease,19.5±7.6% vs 15.8±9.3%). It lengthened the mean RP without a significant increase in the dispersion of refractoriness (standard deviation and range of RP). Sustained VT was induced in 6 of the 7 dogs by ventricular pacing only after the additional doses of FA(FA(2)). FA(2) caused a greater CV slowing in both the L and T fiber orientation (%CV decrease, 48.5±6.9% vs 41.3±5.7%) with further reduction in the ratio of L/T CV. Further the dispersion of refractoriness as well as the mean RP was increased with FA(2).

	Conduction Velocity(m/sec)			Refractory period(msec)		
	L	T	L/T	Mean	SD	Range
Control	0.74±0.10	0.32±0.01	2.31±0.30	175.3	5.5	20.3
FA(1)	0.60±0.09	0.27±0.03	2.22±0.30	199.6	5.9	22.5
FA(2)	0.37±0.07	0.19±0.02	1.98±0.29	213.6	8.2	31.2
						BCL=400msec

In conclusion, FA has"proarrhythmic"effect in the normal canine heart associated with excessive anisotropic conduction slowing and increased disparity of refractoriness.